IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **A. Palani *et al.***	:	
Serial No.: **10/629,466**	:	Examiner: Celia C. Chang
Filed: **July 29, 2003**	:	Group Art Unit: 1625
For: **"PIPERIDINE DERIVATIVES USEFUL AS CCR5 ANTAGONISTS**	:	Date: March 8, 2007

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132 OF MICHAEL W. MILLER, Ph.D.

I, Michael W. Miller, declare as follows:

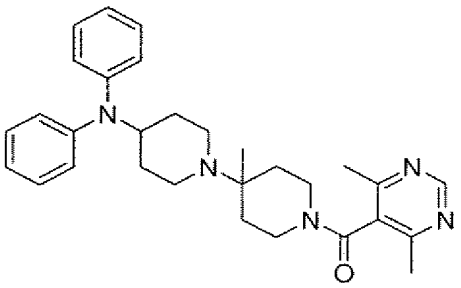
1. I am an inventor of the subject matter claimed in the above-referenced patent application.

2. I received a Ph.D. degree in Chemistry from Colorado State University in 1994. I have been working as a scientist for over 10 years. I am the author of 13 publications, am an inventor in at least 5 granted US patents, have given a number of scientific presentations, and have received numerous honors/awards. Currently, I am employed as a Senior Principal Scientist at Schering-Plough Research Institute. Attached is a copy of my *curriculum vitae* (Exhibit A).

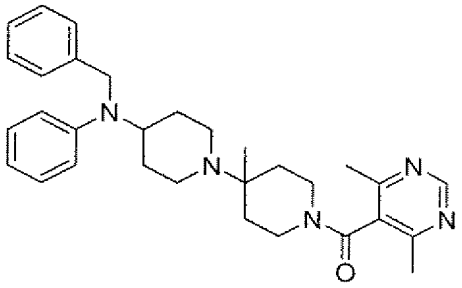
3. I have read the reference (GB 018876.4) at issue in the Office Action dated April 17, 2006 for the above captioned patent application.

4. The experiments set forth herein were either performed by me or by others under my direction and control, at Schering-Plough Research Institute.

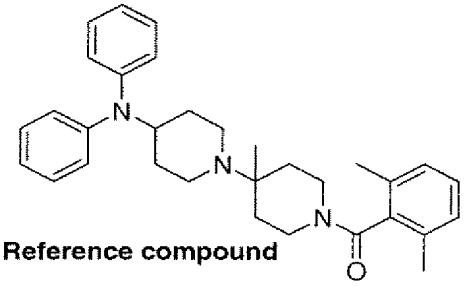
5. The human plasma protein binding and the antiviral IC50 activity of two of the instantly claimed compounds, viz., compounds of examples 9 and 72 (set forth on pages 53 and 72 respectively of the specification of the above captioned application) were compared with those of the compound on page 5 of GB'876.4, the reference under consideration. The structures of the compounds are again set forth below:



Compound of Example 72



Compound of Example 9



Reference compound

6. Human plasma protein binding for the three compounds was determined by equilibrium dialysis. The dialysis chambers for plasma and buffer are separated by a semi permeable membrane (10 KD cutoff), which allows only small molecules to diffuse between two chambers. The compound was spiked in plasma at an initial concentration at 10 μM. After 20 hr incubation at

37 °C, compound concentrations in plasma (Cp) and buffer (Cb) were measured by LC/MS/MS. The % bound was calculated as: % bound = [(Cp-Cb)/(Cp)] x 100.

7. Table 1 shows the results of the human plasma protein binding experiments:

Table 1

Human Plasma Protein Binding

Compound	% Bound
Example 72	89.5
Example 9	92.1
Reference	99.6

8. The results in Table 1 indicate that the claimed compounds of Example 72 and Example 9 display lower human plasma protein binding and are therefore likely to exhibit increased *in-vivo* activity at the desired target receptor.

9. To determine the effects of serum on the activity of compounds, the luciferase replication assay described on pages 45-46 of the specification was modified as follows: U-87-CCR5 cells were plated 96-well plates one day before infection. On the day of infection, culture media was removed and replaced with 90 μl of culture media containing 0, 5%, 10% 20% or 40% normal human serum. Test compounds were diluted in culture media and 10 μl added to cells in triplicate wells. Cells were incubated with compound and serum for 1 hour prior to infection with an HIV-1-luciferase virus. Infections were allowed to proceed for 3 days after which time the supernatant was removed, cells lysed and

luciferase activity measured. Data was plotted as % of control and IC50 values determined using the GraphPad prism software program.

10. Table 2 shows the antiviral activity of the test compounds in the presence of varying amounts of human serum:

Table 2

Antiviral IC50 (nM) of test compounds

(Luciferase Assay)

Human Serum %	Compound of Example 9	Compound of Example 72	Reference compound
0	0.52	0.95	0.90
5%	0.25	1.2	2.2
10%	0.64	2.2	2.7
20%	1.2	6.0	11
40%	1.7	32	44

11. The data in Table 2 shows that there is a much greater shift in antiviral activity of the compound of Example 72 and the reference compound (30-40 fold increase) versus that with compound of Example 9 (3-4 fold increase) in the presence of 40 % human serum. This reduction of activity of various agents in the presence of human serum has been noted in the literature[1] , and this feature is likely to be important in the pharmacology of these agents in humans.

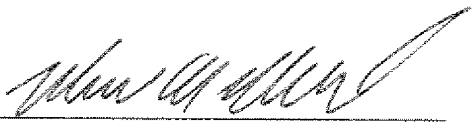
[1] See a) Molla, A., Vasavanonda, S., Kumar, G., Sham, H.L., Johnson, M., Grabowski, B., Denissen, J.F., Kohlbrenner, W., Plattner, J.J., Leonard, J.M., Norbeck, D.W., Kempf, D.J. *Virology*, **1998**, *250*, 255-262; b) Peterson, L.R., Moody, J.A., Fasching, C.E., Gerding, D.N. *Antimicrob. Agents Chemother.* **1989**, *33*, 566-568.

From this data, compound of Example 9 would be favored based on the reduced plasma protein binding and reduced shift in antiviral activity in human plasma. This compound should be expected to interact with the desired receptor (CCR5) with higher efficiency *in-vivo*. Structurally, this compound corresponds to presently claimed Formula I wherein R^2 is arylalkyl and R^3 is substituted pyrimidine. Thus, present compounds with these structural features are expected to have unexpected beneficial features, as shown by the compound of Example 9. Furthermore, these structural features are absent from the reference compound.

12. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application and any patent issued thereon.

3/18/07

Date



Michael W. Miller, Ph. D.